VIRA-A - vidarabine monohydrate ointment
Monarch Pharmaceuticals, Inc.

DESCRIPTION

VIRA-A is the trade name for vidarabine (also known as adenine arabinoside and Ara-A), an antiviral drug for the topical treatment of epithelial keratitis caused by Herpes simplex virus. The chemical name is 9H-Purin-6-amine, 9-β-D-arabinofuranosyl-, monohydrate.

Each gram of the ophthalmic ointment contains 30 mg of vidarabine monohydrate equivalent to 28.11 mg of vidarabine in a sterile, inert, petrolatum base.

The empirical and structural formulas are:

CLINICAL PHARMACOLOGY

VIRA-A is rapidly deaminated to arabinosylhypoxanthine (Ara-Hx), the principal metabolite. Ara-Hx also possesses *in vitro* antiviral activity but this activity is less than that of VIRA-A. Because of the low solubility of VIRA-A, trace amounts of both VIRA-A and Ara-Hx can be detected in the aqueous humor only if there is an epithelial defect in the cornea. If the cornea is normal, only trace amounts of Ara-Hx can be recovered from the aqueous humor.

Systemic absorption of VIRA-A should not be expected to occur following ocular administration and swallowing lacrimal secretions. In laboratory animals, VIRA-A is rapidly deaminated in the gastrointestinal tract to Ara-Hx.

In contrast to topical idoxuridine, VIRA-A demonstrated less cellular toxicity in the regenerating corneal epithelium of the rabbit. In controlled and uncontrolled clinical trials, an average of seven and nine days of continuous VIRA-A Ophthalmic Ointment, 3%, therapy was required to achieve corneal re-epithelialization. In the controlled trials, 70 of 81 subjects (86%) re-epithelialized at the end of three weeks of therapy. In the uncontrolled trials, 101 of 142 subjects (71%) re-epithelialized at the end of three weeks. Seventy-five percent of the subjects in these uncontrolled trials had either not healed previously or had developed hypersensitivity to topical idoxuridine therapy.

Microbiology

Vidarabine is a purine nucleoside obtained from fermentation cultures of *Streptomyces antibioticus*. The antiviral mechanism of action has not been established. Vidarabine appears to interfere with the early steps of viral DNA synthesis.

Vidarabine has been shown to possess antiviral activity against the following viruses *in vitro:*

Herpes simplex types 1 and 2
Vaccinia
Varicella-Zoster

Except for Rhabdovirus and Oncornavirus, vidarabine does not display *in vitro* antiviral activity against other RNA or DNA viruses, including Adenovirus.

Susceptibility Tests - No universal, standardized, quantitative *in vitro* procedures have as yet been developed to estimate the susceptibility of viruses to antiviral agents.

INDICATIONS AND USAGE

VIRA-A Ophthalmic Ointment, 3%, is indicated for the treatment of acute keratoconjunctivitis and recurrent epithelial keratitis due to Herpes simplex virus types l and 2. The clinical diagnosis of keratitis caused by Herpes simplex virus is usually established by the presence of typical dendritic or geographic lesions on slit-lamp examination. It is also effective in superficial keratitis caused by Herpes simplex virus which has not responded to topical idoxuridine or when toxic or hypersensitivity reactions due to idoxuridine have occurred. The effectiveness of VIRA-A Ophthalmic Ointment, 3%, against stromal keratitis and uveitis due to Herpes simplex virus has not been established.

CONTRAINDICATIONS

VIRA-A Ophthalmic Ointment, 3%, is contraindicated in patients who develop hypersensitivity reactions to it.

WARNINGS

Normally, corticosteroids alone are contraindicated in Herpes simplex virus infections of the eye. If VIRA-A Ophthalmic Ointment, 3%, is administered concurrently with topical corticosteroid therapy, corticosteroid-induced ocular side effects must be considered. These include corticosteroid-induced glaucoma or cataract formation and progression of a bacterial or viral infection.

VIRA-A is not effective against RNA virus or adenoviral ocular infections. It is also not effective against bacterial, fungal, or chlamydial infections of the cornea or nonviral trophic ulcers.

Although viral resistance to VIRA-A has not been observed, this possibility may exist.

PRECAUTIONS

General
The diagnosis of keratoconjunctivitis due to Herpes simplex virus should be established clinically prior to prescribing VIRA-A Ophthalmic Ointment, 3%.
Patients should be forewarned that VIRA-A Ophthalmic Ointment, 3%, like any ophthalmic ointment, may produce a temporary visual haze.

Carcinogenesis
Chronic parenteral (IM) studies of vidarabine have been conducted in mice and rats.
In the mouse study, there was a statistically significant increase in liver tumor incidence among the vidarabine-treated females. In the same study some vidarabine-treated male mice developed kidney neoplasia. No renal tumors were found in the vehicle-treated control mice or the vidarabine-treated female mice.
In the rat study, intestinal, testicular, and thyroid neoplasia occurred with greater frequency among the vidarabine-treated animals than in the vehicle-treated controls. The increases in thyroid adenoma incidence in the high-dose (50 mg/kg) males and the low-dose (30 mg/kg) females were statistically significant.
Hepatic megalocytosis, associated with vidarabine treatment, has been found in short and long-term rodent (rat and mouse) studies. It is not clear whether or not this represents a preneoplastic change.
The recommended frequency and duration of administration should not be exceeded (see DOSAGE AND ADMINISTRATION).

Mutagenesis
Results of *in vitro* experiments indicate that vidarabine can be incorporated into mammalian DNA and can induce mutation in mammalian cells (mouse L5178Y cell line). Thus far, *in vivo* studies have not been as conclusive, but there is some evidence (dominant lethal assay in mice) that vidarabine may be capable of producing mutagenic effects in male germ cells.
It has also been reported that vidarabine causes chromosome breaks and gaps when added to human leukocytes *in vitro.* While the significance of these effects in terms of mutagenicity is not fully understood, there is a well-known correlation between the ability of various agents to produce such effects and their ability to produce heritable genetic damage.

Pregnancy Category C
VIRA-A parenterally is teratogenic in rats and rabbits. Ten percent VIRA-A ointment applied to 10% of the body surface during organogenesis induced fetal abnormalities in rabbits. When 10% VIRA-A ointment was applied to 2% to 3% of the body surface of rabbits, no fetal abnormalities were found. This dose greatly exceeds the total recommended ophthalmic dose in humans. The possibility of embryonic or fetal damage in pregnant women receiving VIRA-A Ophthalmic Ointment, 3%, is remote. The topical ophthalmic dose is small, and the drug relatively insoluble. Its ocular penetration is very low. However, a safe dose for a human embryo or fetus has not been established. There are no adequate and well-controlled studies in pregnant women. VIRA-A should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
It is not known whether VIRA-A is secreted in human milk. Because many drugs are excreted in human milk and because of the potential for tumorigenicity shown for VIRA-A in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. However, breast milk excretion is unlikely because VIRA-A is rapidly deaminated in the gastrointestinal tract.

Pediatric Use
The safety and effectiveness in pediatric patients below the age of 2 years have not been established.

ADVERSE REACTIONS
Lacrimation, foreign body sensation, conjunctival injection, burning, irritation, superficial punctate keratitis, pain, photophobia, punctal occlusion, and sensitivity have been reported with VIRA-A Ophthalmic Ointment, 3%. The following have also been reported but appear disease-related: uveitis, stromal edema, secondary glaucoma, trophic defects, corneal vascularization, and hyphema.

OVERDOSAGE
Acute massive overdosage by oral ingestion of the ophthalmic ointment has not occurred. However, the rapid deamination to arabinosylhypoxanthine should preclude any difficulty. The oral LD_{50} for vidarabine is greater than 5020 mg/kg in mice and rats. No untoward effects should result from ingestion of the entire contents of the tube.
Overdosage by ocular instillation is unlikely because any excess should be quickly expelled from the conjunctival sac.

DOSAGE AND ADMINISTRATION
Administer approximately one-half inch of VIRA-A Ophthalmic Ointment, 3%, into the lower conjunctival sac five times daily at three-hour intervals.

If there are no signs of improvement after 7 days, or complete re-epithelialization has not occurred by 21 days, other forms of therapy should be considered. Some severe cases may require longer treatment.
Too frequent administration should be avoided.
After re-epithelialization has occurred, treatment for an additional 7 days at a reduced dosage (such as twice daily) is recommended in order to prevent recurrence.
The following topical antibiotics: gentamicin, erythromycin, chloramphenicol; or topical steroids: prednisolone or dexamethasone have been administered concurrently with VIRA-A Ophthalmic Ointment, 3%.

HOW SUPPLIED
NDC 61570-367-71
VIRA-A Ophthalmic Ointment, 3%, is supplied sterile in ophthalmic ointment tubes of 3.5 g. The base is a 60:40 mixture of solid and liquid petrolatum.
Store at room temperature 15°–30°C (59°F–86°F).
Rx only.
Distributed by: Monarch Pharmaceuticals, Inc., Bristol, TN 37620
Manufactured by: Parkedale Pharmaceuticals, Inc., Rochester, MI 48307